Session 7: Clinical variability in Sickle Cell Disease

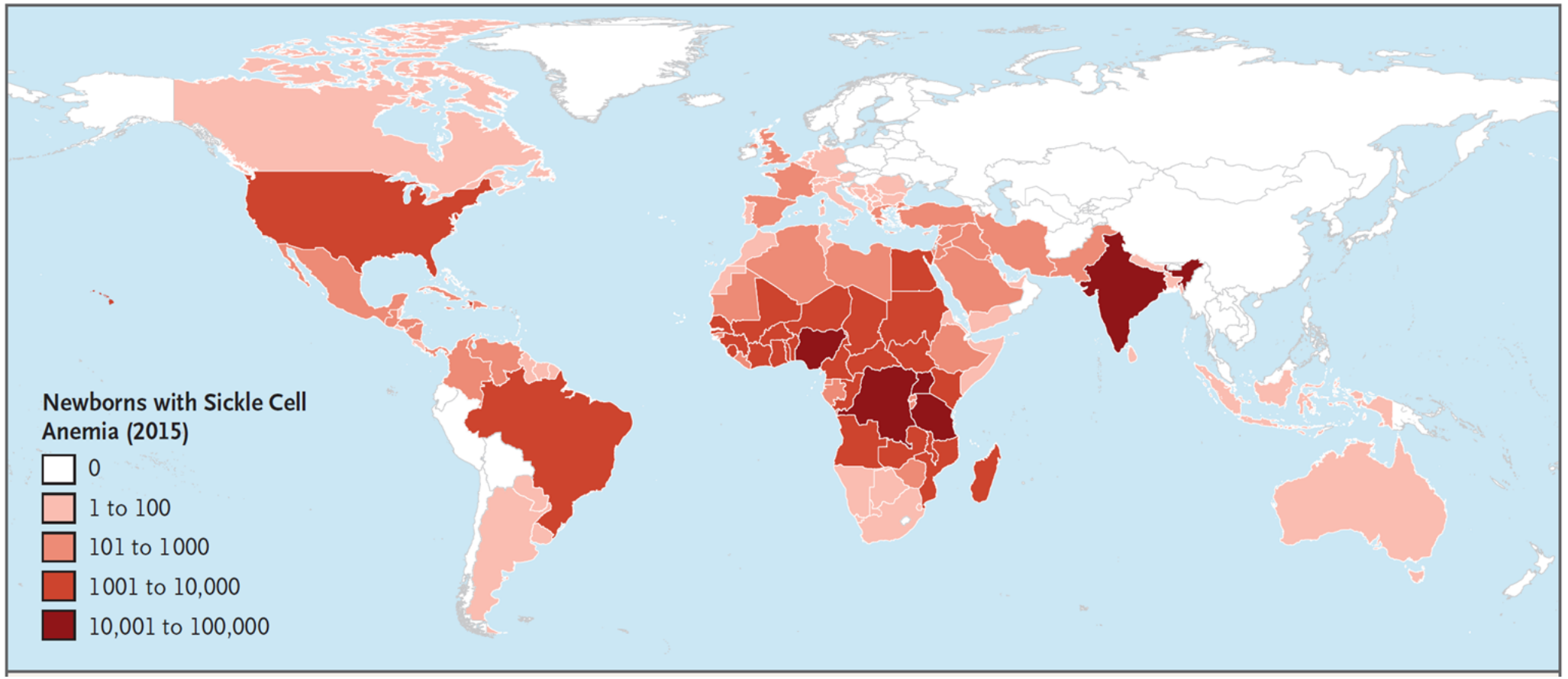
Global variability of sickle cell disease severity, mortality and morbidity

Dr Frédéric B. Piel

School of Public Health, Imperial College London

Paris, 16th June 2022

Sickle cell disease: a global disease



Piel, Rees & Steinberg, *NEJM* 2017

Imperial College London

Sickle cell disease: an inequal burden

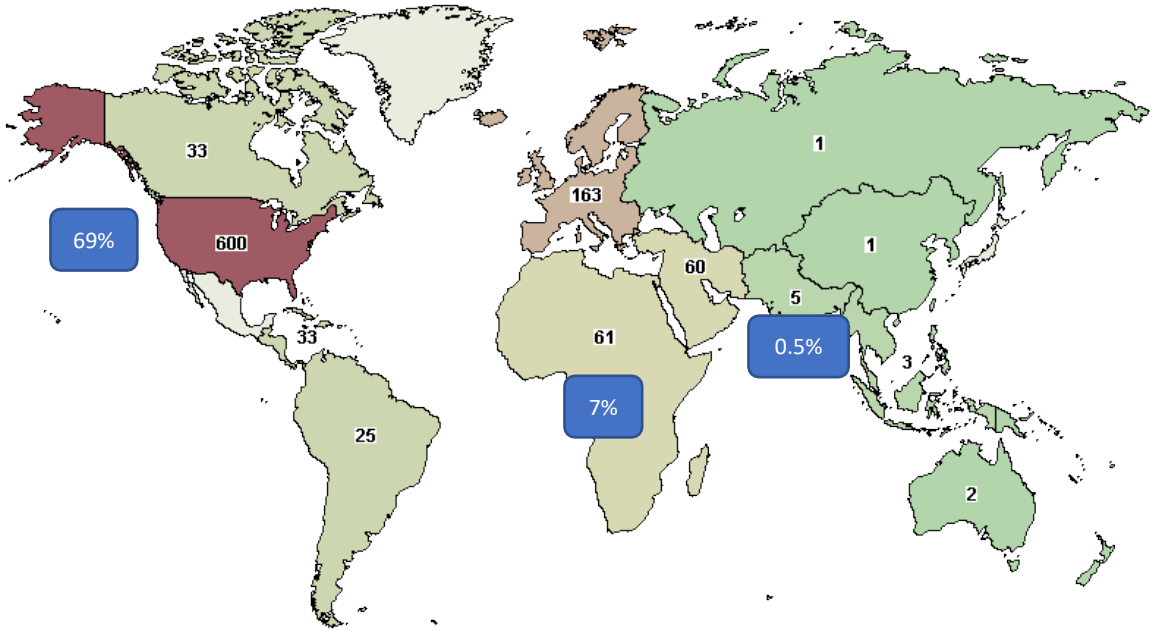
Category	Sub-Category	2010		
		Number of Newborns with SCA[a]	CI[b]	Percent of Category
Country	Nigeria	91,011	[77,881–106,106]	29.8%
	India	44,425	[33,692–59,143]	14.5%
	DRC	39,743	[32,593–48,788]	13.0%
WHO region[e]	AFRO	237,381	[191,067–295,354]	77.6%
	AMRO	11,143	[6,305–19,823]	3.6%
	EMRO	10,559	[6,242–19,390]	3.5%
	EURO	1,939	[932–4,330]	0.6%
	SEARO	44,454	[33,696–59,338]	14.5%
	WPRO	6	[1–23]	0.0%
HbS region[f]	Eurasia	5,130	[2,474–11,179]	1.7%
	Americas	11,181	[6,324–19,896]	3.7%
	Sub-Saharan Africa	242,187	[194,549–302,012]	79.2%
	Southeast Asia	7	[1–32]	0.0%
	Arab-India	47,264	[35,050–65,640]	15.5%
World		305,773	[238,400–398,775]	100%

NIH U.S. National Library of Medicine

ClinicalTrials.gov

All registered studies for sickle cell disease

(n=868)



Piel *et al* 2013, *PLOS Medicine*

Imperial College London

Variability of SCD severity

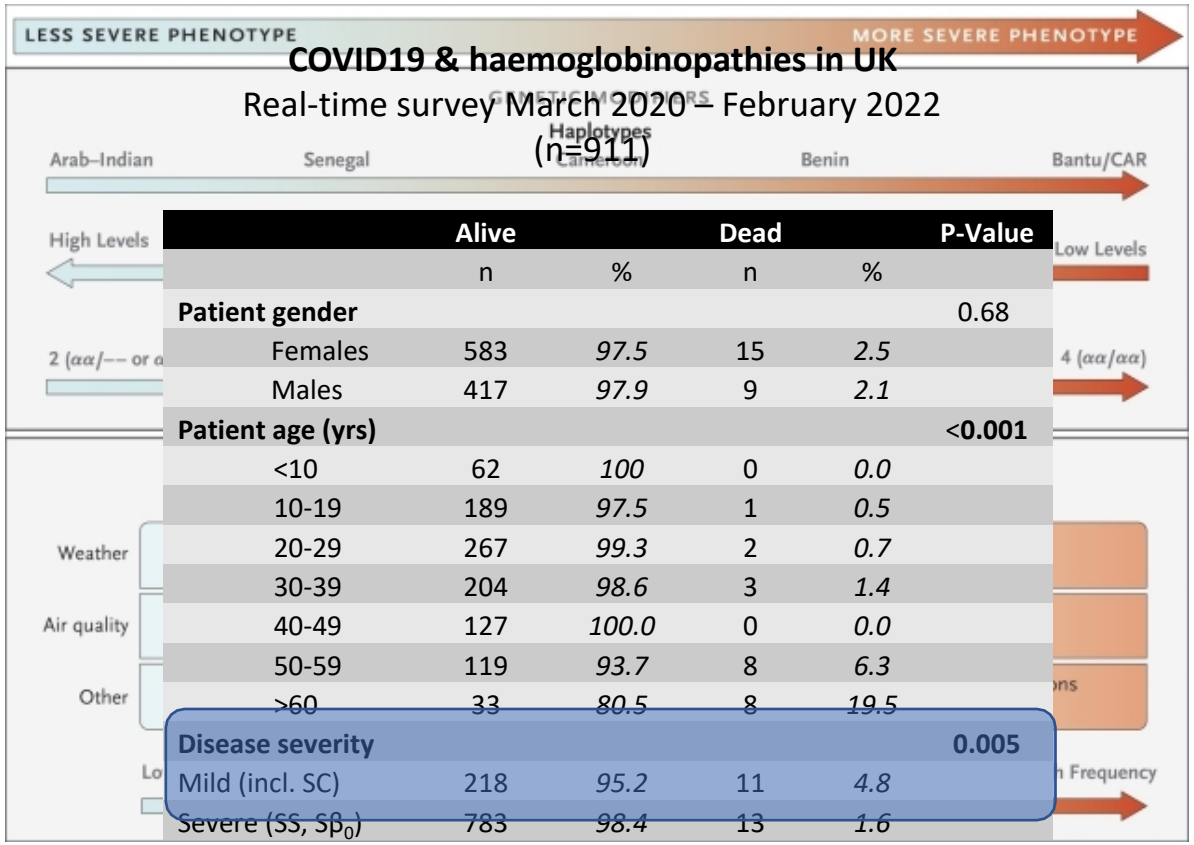
Exp Biol Med (Maywood). 2016 April ; 241(7): 679–688. doi:10.1177/1535370216640385.

Clinical severity in sickle cell disease: the challenges of definition and prognostication

Charles T. Quinn
Division of Hematology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45220, USA

Abstract

Sickle cell disease (SCD) is a monogenic, yet highly phenotypically variable disease with multisystem pathology. This manuscript provides an overview of many of the known determinants, modifiers, and correlates of disease severity in SCD. Despite this wealth of data, modeling the variable and multisystem pathology of SCD continues to be difficult. The current status of prediction of specific adverse outcomes and global disease severity in SCD is also reviewed, highlighting recent successes and ongoing challenges.



COVID19 & haemoglobinopathies in UK
Real-time survey March 2020 – February 2022
(n=911)

	Alive		Dead		P-Value
	n	%	n	%	
Patient gender					0.68
Females	583	*97.5*	15	*2.5*	
Males	417	*97.9*	9	*2.1*	
Patient age (yrs)					**<0.001**
<10	62	*100*	0	*0.0*	
10-19	189	*97.5*	1	*0.5*	
20-29	267	*99.3*	2	*0.7*	
30-39	204	*98.6*	3	*1.4*	
40-49	127	*100.0*	0	*0.0*	
50-59	119	*93.7*	8	*6.3*	
>60	33	*80.5*	8	*19.5*	
Disease severity					**0.005**
Mild (incl. SC)	218	*95.2*	11	*4.8*	
Severe (SS, $S\beta_0$)	783	*98.4*	13	*1.6*	

Piel, Rees & Steinberg, *NEJM* 2017
Layton *et al* 2022, *Unpublished*

Global variability of SCD severity

Exp Biol Med (Maywood). 2016 April ; 241(7): 679–688. doi:10.1177/1535370216640385.

Clinical severity in sickle cell disease: the challenges of definition and prognostication

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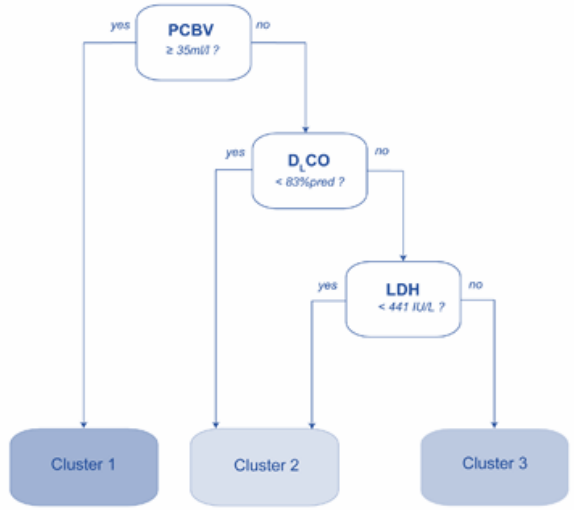
Division of Hematology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45220, USA

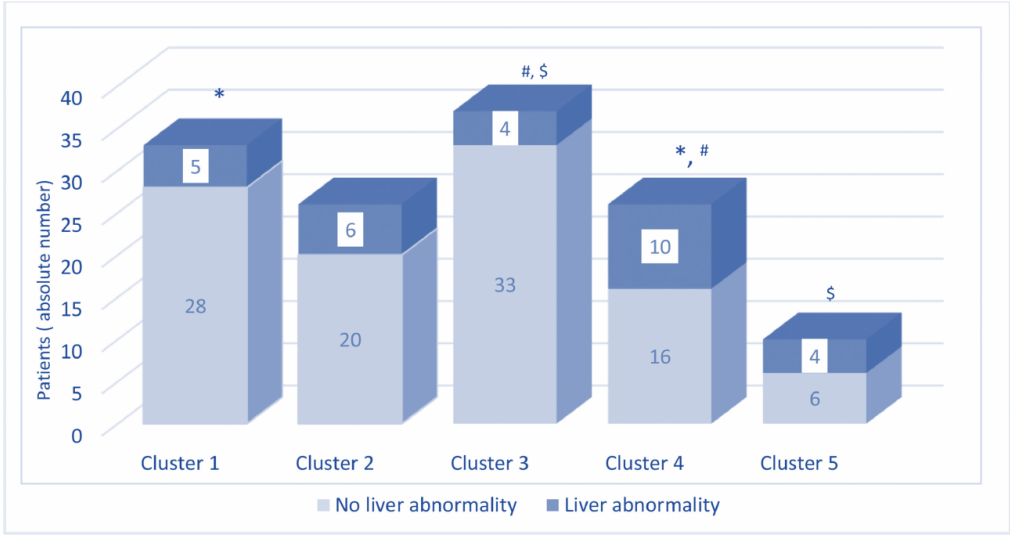
[...] "the prediction of single, distinct adverse outcomes, like overt stroke, remains easier than prediction of globally severe SCD."

Cluster analysis and lung function in SCD (UK)



Lunt *et al* 2018, *Thorax*

Hierarchical cluster analysis (Brazil)



De Freitas Dutra *et al* 2021, *Hematol. Transfus. Cell. Ther*

Variability of SCD severity

Exp Biol Med (Maywood). 2016 April ; 241(7): 679–688. doi:10.1177/1535370216640385.

Clinical severity in sickle cell disease: the challenges of definition and prognostication

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"Sophisticated and comprehensive modeling that incorporates "multi-omic" (e.g. genomic, proteomic, and metabolomic) factors may advance this effort."

ASH 2018

113. HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIA-BASIC AND TRANSLATIONAL SCIENCE: POSTER III | NOVEMBER 29, 2018

Proteomics Pathways of Sickle Cell Anemia (P2SCA): A Comprehensive Analysis By Liquid Chromatography Mass Spectrometry of Erythrocyte Membrane Proteins Characterized from the Muhimbili Sickle Cell Programme, Tanzania

Haddy KS Fye, PhD BSc, Paul Mrosso, Frédéric B Piel, PhD, Simon Davis, Roman Fischer, Gration Rwegasira, Benedikt Kessler, Julie Makani, MD PhD FRCP

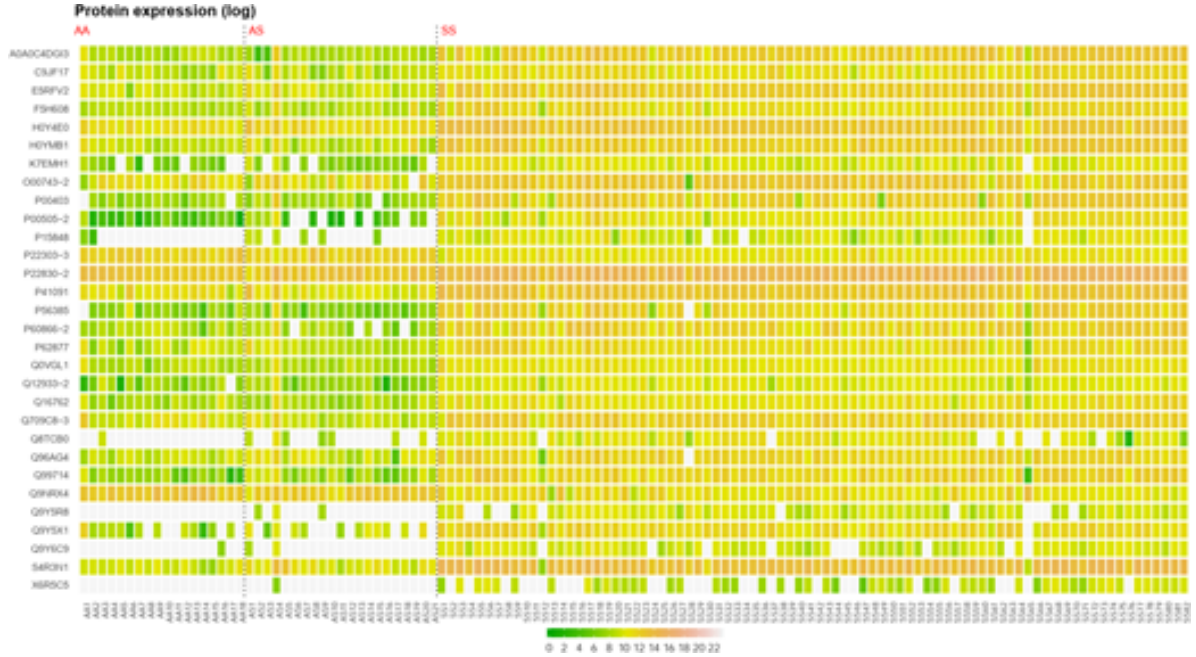
American Thoracic Society International Conference 2020

D59 SICKLE CELL DISEASE / Thematic Poster Session

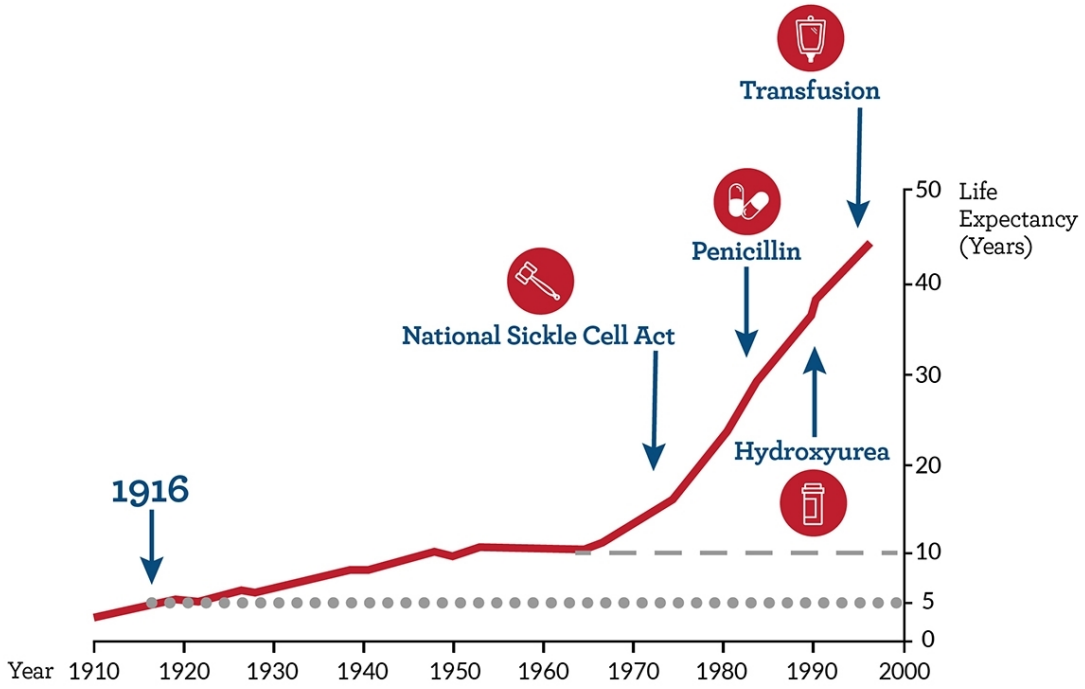
Multi-Omics Profiling of Sickle Cell Acute Chest Syndrome

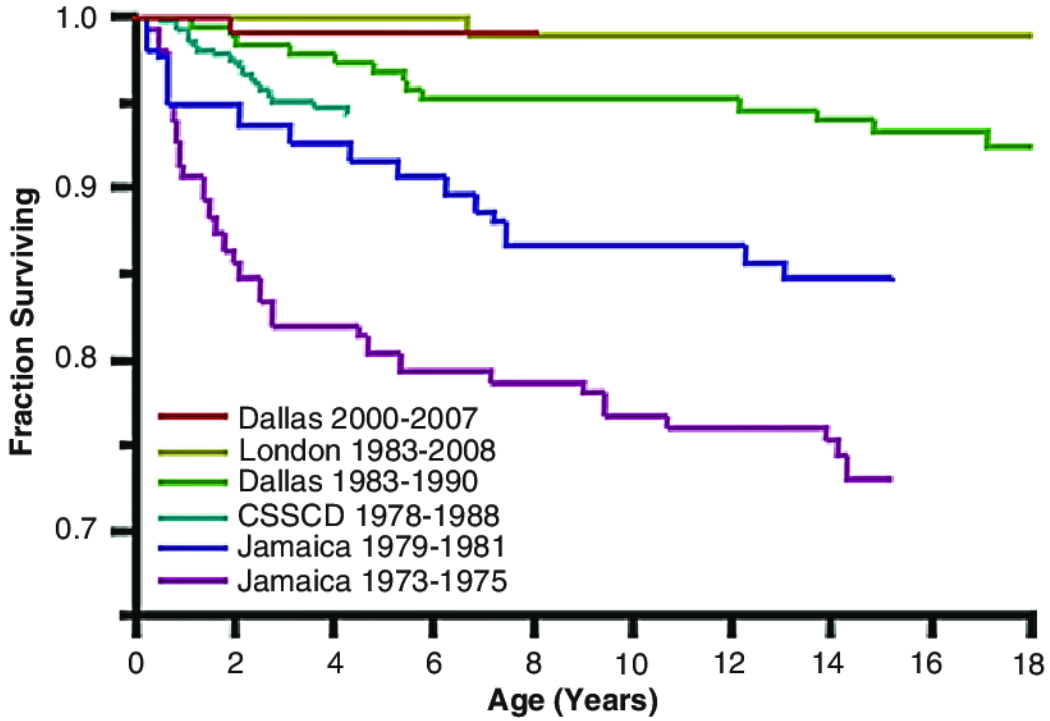
B. T. Kopp, S. Creary, B. Loman, C. Shrestha, K. Kotha, A. Minta, S. Zhang, S. J. Pinto, R. A. Thompson, O. Ramilo, P. White, M. Bailey, A. Mejias; Nationwide Childrens Hosp, Columbus, OH, United States.

Corresponding author's email: benjamin.kopp@nationwidechildrens.org

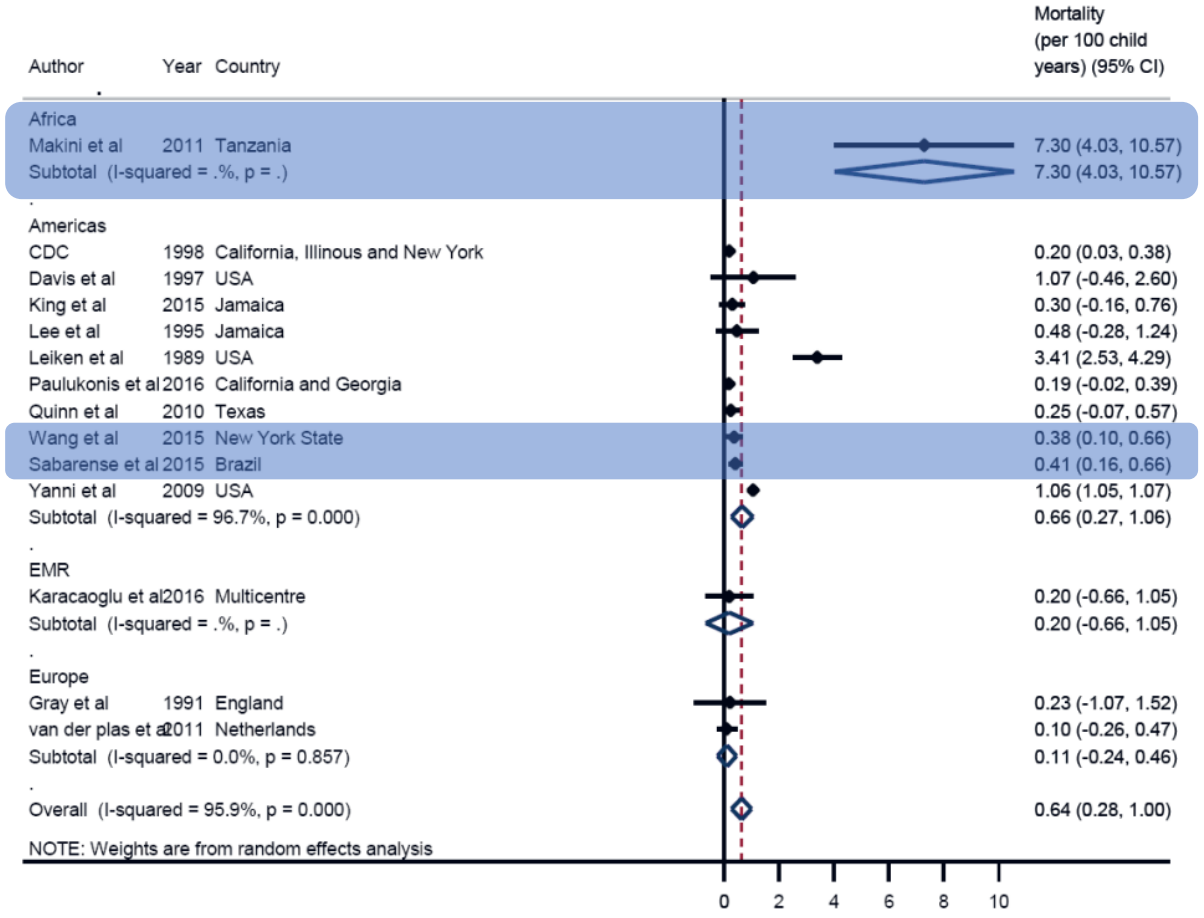


Spatio-temporal variability of SCD mortality





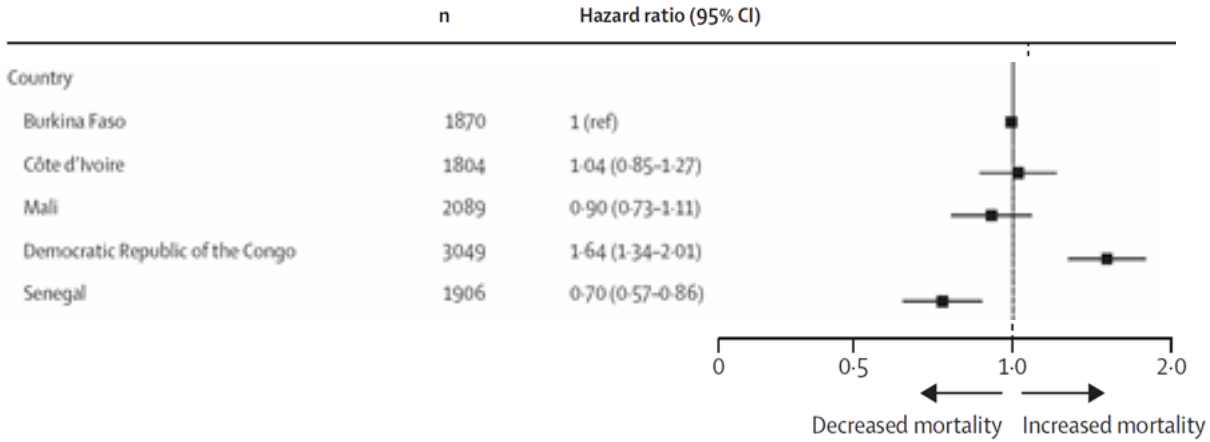
Global variability of SCD mortality



Wastenedge *et al* 2018, *Journal of Global Health*

BIOCADRE Study – 5 African countries

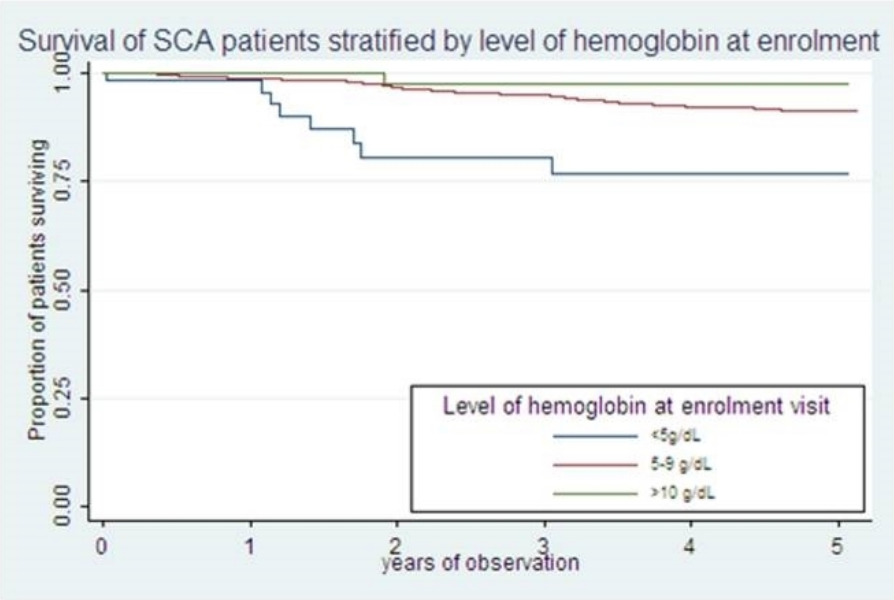
Multivariate survival model for children younger than 15 years



Ranque *et al* 2022, *The Lancet Haematology*

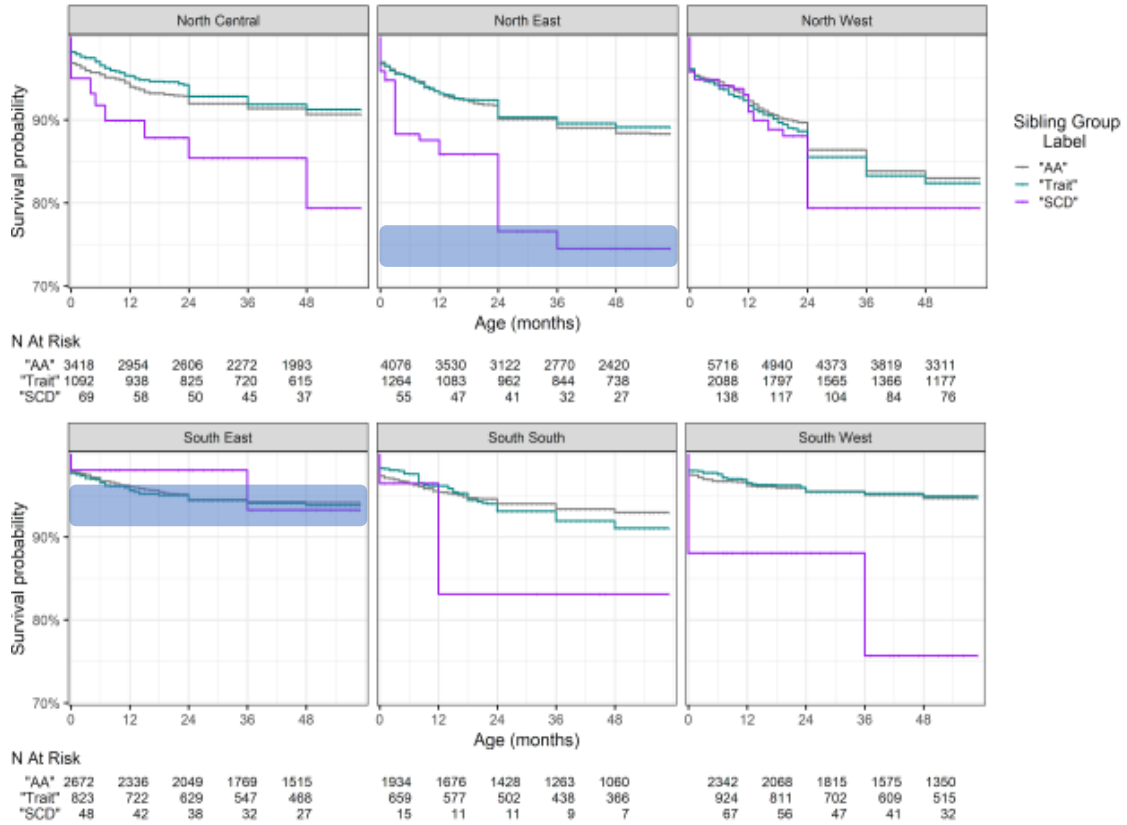
Global variability of SCD mortality

Muhimbili National Hospital (MNH), Dar-es-Salaam, Tanzania



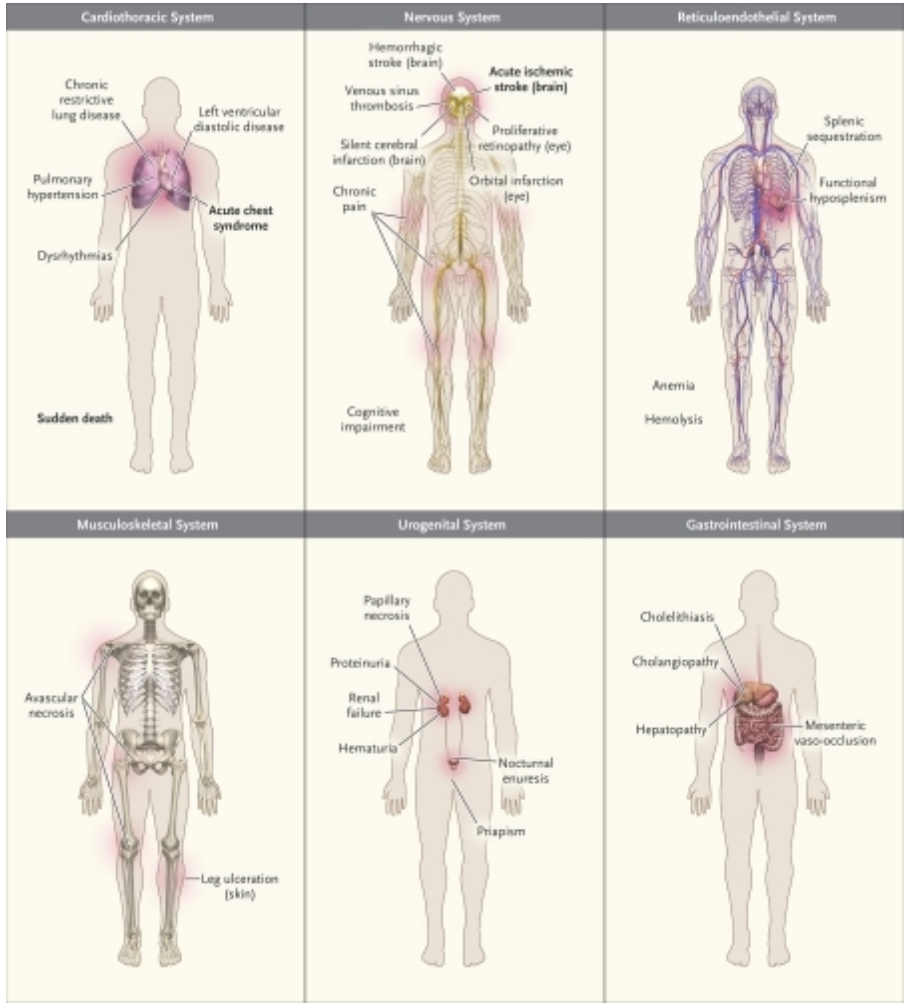
"In low- and middle-income countries, few studies have explored availability of resources for care of SCD showing widespread limitation where all too often resources are **limited to private facilities** and beyond the reach of the majority who would benefit"

Makani *et al* 2011, *PLOS One; Makani et al* 2018, *Front. Genet.*



Nnodu *et al* 2021, *The Lancet Haematology*

Global variability of SCD morbidity



Piel, Rees & Steinberg, *NEJM* 2017

Global variability of SCD morbidity: Pain

ELSEVIER

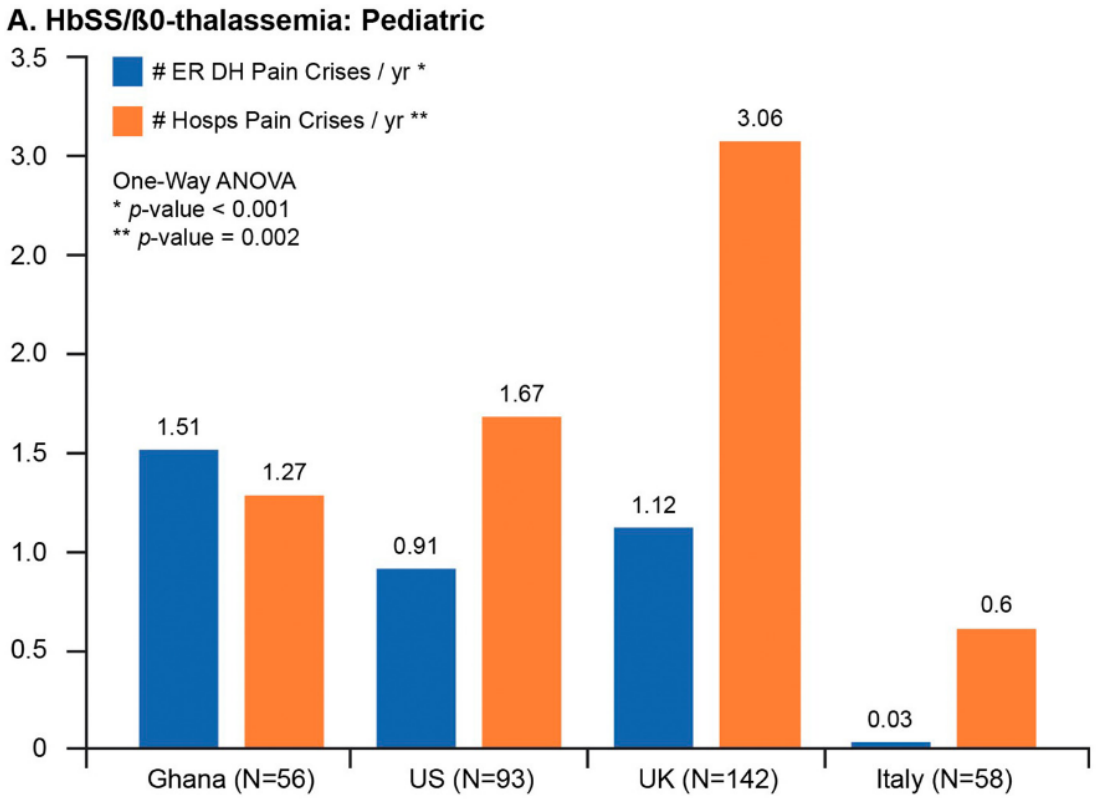
Blood Cells, Molecules, and Diseases

Volume 92, December 2021, 102612

Global geographic differences in healthcare utilization for sickle cell disease pain crises in the CASiRe cohort

Crawford Strunk [e], Immacolata Tartaglione [c], Connie M. Piccone [i], Raffaella Colombatti [a], Biree Andemariam [b], Deepa Manwani [f], Ashya Smith [n], Haikel Haile [n], Esther Kim [n], Samuel Wilson [n], Eugenia Vicky Asare [g], Angela Rivers [h], Fatimah Farooq [n], Rebekah Urbonya [n], Donna Boruchov [j], Gifty Dankwah Boatemaa [d], Silverio Perrotta [c], Ivy Ekem [g] ... Andrew D. Campbell [n, o]

n=868



Global variability of SCD morbidity: Stroke

Journal of Clinical Medicine
MDPI

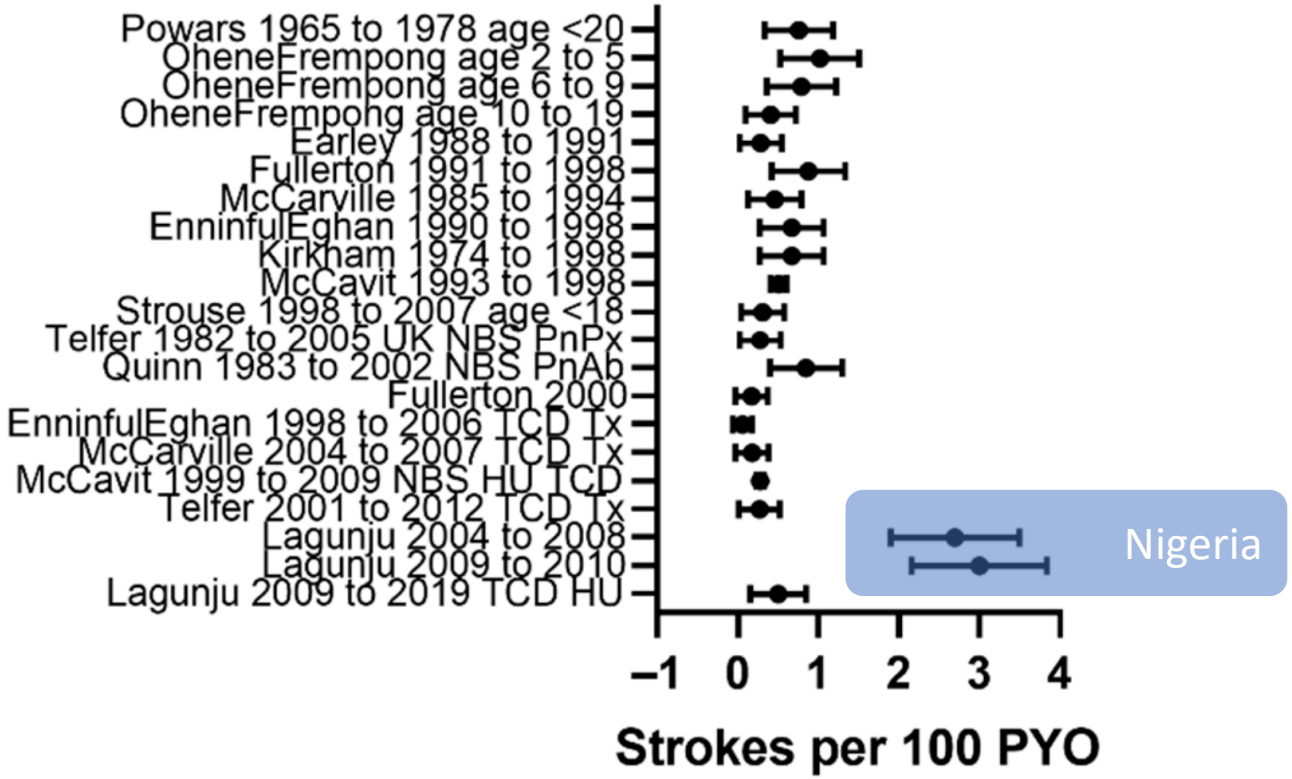
Review

Epidemiology of Stroke in Sickle Cell Disease

Fenella Jane Kirkham [1,2,3,*] and Ikeoluwa A. Lagunju [4,5]

1 Developmental Neurosciences, UCL Great Ormond Street Institute of Child Health, Faculty of Population Health Sciences, 30 Guilford Street, London WC1N 1EH, UK
2 Child Health, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton and University Hospital Southampton, Southampton SO16 6YD, UK
3 Paediatric Neurosciences, King's College Hospital, London SE5 9RS, UK
4 Department of Paediatrics, College of Medicine, University of Ibadan, Ibadan PMB 3017, Nigeria; ilagunju@yahoo.co.uk
5 Department of Paediatrics, University College Hospital, Ibadan PMB 5116, Nigeria
* Correspondence: Fenella.Kirkham@ucl.ac.uk

"Without any screening or preventative treatment, the incidence appears to fall within the range 0.5 to 0.9 per 100 patient years of observation."



Global variability of SCD morbidity: ACS

blood

ARTICLES | JULY 15, 1994

The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease

O Castro, DJ Brambilla, B Thorington, CA Reindorf, RB Scott, P Gillette, JC Vera, PS Levy

n=3,751

"ACS incidence was higher in patients with homozygous sickle cell disease (SS; **12.8/100 pt-yrs**) and in patients with sickle cell-beta(0) -thalassemic (9.4/100 pt-yrs), and lower in patients with hemoglobin (Hb) SC disease (5.2/100 pt-yrs) and patients with sickle cell-beta(+) thalassemia (3.9/100 pt-yrs)."

Transactions of the Royal Society of
Tropical Medicine & Hygiene

REVIEW

Managing acute chest syndrome of sickle cell disease in an African setting

A.E. Fawibe*

Department of Internal Medicine, Federal Medical Center, Bida, Niger State, Nigeria

Received 2 December 2007; received in revised form 17 March 2008; accepted 19 March 2008

"[…] there are no firm data on its incidence in Nigeria. It was present in **6%** of 102 adolescents and adults in a monocentric study conducted in Lagos, Nigeria. However, studies done elsewhere have shown that it is a common complication that occurs in about **50%** of patients with SCA and is recurrent in about **80%** of them."

Multicenter Study > Pan Afr Med J. 2022 Feb 3;41:97. doi: 10.11604/pamj.2022.41.97.29629. eCollection 2022.

Clinical profile of sickle cell disease in children treated at "Cliniques Universitaires de Bukavu" and "Clinique Ami des Enfants", Bukavu, Democratic Republic of the Congo

Viviane Feza Bianga [1 2], Mwanza Nangunia [3], Fernand Manga Oponjo [1 2], John Mambo Itongwa [1 2 4], Judicaël Iragi Mushubusha [1], Moise Mbaluku Colombe [1 2 4], Carmel Mbalo Walemba [1 4], Okitosho Wembonyama [5]

"acute chest syndrome was only found in 9.1%."

Global variability of SCD morbidity: Leg ulcers

Am J Hematol. 2010 October ; 85(10): 831–833. doi:10.1002/ajh.21838.

Leg Ulcers in Sickle Cell Disease

Caterina P. Minniti[1], **James Eckman**[3], **Paola Sebastiani**[4], **Martin H. Steinberg**[5], and **Samir K. Ballas**[2]

Caterina P. Minniti: Minnitic@mail.nih.gov

[1] Pulmonary Vascular Medicine Branch, NHLBI, National Institutes of Health, Bethesda, MD

[2] Cardeza Foundation for Hematologic Research, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA Samir K. Ballas MD, FACP

[3] Professor of Hematology, Oncology and Medicine, Winship Cancer Institute, Emory University School of Medicine

[4] Department of Biostatistics, Boston University School of Public Health, and Center of Excellence in Sickle Cell Disease, Boston Medical Center

[5] Department of Medicine, Boston University School of Medicine

"Its geographical distribution is also variable, affecting **75%** of HbSS patients in Jamaica but only **8–10%** of North American patients."

OPEN ACCESS PEER-REVIEWED CHAPTER

Leg Ulceration in Sickle Cell Disease: An Early and Visible Sign of End-Organ Disease

WRITTEN BY

Aditi P. Singh and Caterina P. Minniti

Submitted: January 20th, 2016 , Reviewed: May 13th, 2016 , Published: November 10th, 2016

DOI: 10.5772/64234

"Among patients who have the Asian haplotype, leg ulceration is rare [**~1%]** among adults in both the eastern province of Saudi Arabia and central India "

"Though not yet defined, environmental, socioeconomic, and genetic factors are most likely responsible for the variations in incidence."

Imperial College London

Global variability of SCD morbidity

Sickle Cell World Assessment Survey (SWAY): survey: 16 countries, ~2,500 patients.

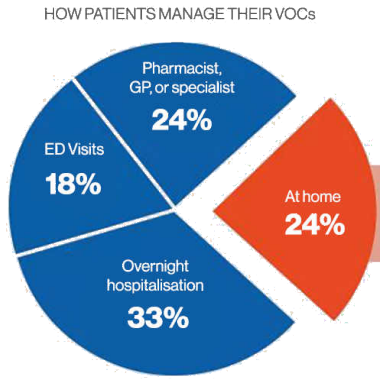
OMICS A Journal of Integrative Biology
Volume 24, Number 10, 2020
Mary Ann Liebert, Inc.
DOI: 10.1089/omi.2020.0153

Review Article

The Sickle Cell Disease Ontology: Enabling Collaborative Research and Co-Designing of New Planetary Health Applications

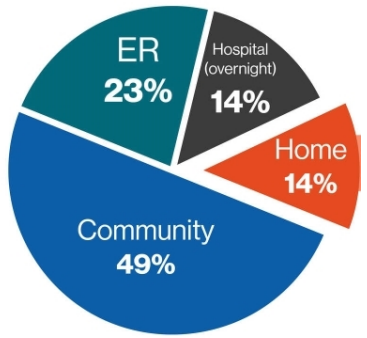
Victoria Nembaware,[1] Gaston K. Mazandu,[1] Jade Hotchkiss,[1] Jean-Michel Safari Serufuri,[1] Jill Kent,[2] Andre Pascal Kengne,[3] Kofi Anie,[4,5] Nchangwi Syntia Munung,[1] Daima Bukini,[2] Valentina Josiane Ngo Bitoungui,[6] Deogratias Munube,[7] Uzima Chirwa,[8] Catherine Chunda-Liyoka,[8] Agnes Jonathan,[2] Miriam V. Flor-Park,[9] Kevin Kum Esoh,[10] Mario Jonas,[1] Khuthala Mnika,[1] Chandré Oosterwyk,[1] Upendo Masamu,[2] Jack Morrice,[1] Annette Uwineza,[11] Arthemon Nguweneza,[1] Kambe Banda,[1] Isaac Nyanor,[12] David Nana Adjei,[5] Nathan Edward Siebu,[5] Malula Nkanyemka,[2] Patience Kuona,[13] Bamidele O. Tayo,[14] Andrew Campbell,[15] Assaf P. Oron,[16,*] Obiageli E. Nnodu,[17] Vivian Painstil,[18] Julie Makani,[2] Nicola Mulder,[19] and Ambroise Wonkam[1]; on behalf of the Sickle Cell Disease Ontology Working Group

Overall



n~2,500

SA, Bahrain, Oman & Lebanon



n=164

In the Netherlands[5]

It has been reported that:

~68% of VOCs are treated at home*

In the United States[6]

It has been reported that:

~79% of VOCs are treated at home†

Imperial College London

Variability of SCD comorbidity

3-28-2018

Comorbidities in aging patients with sickle cell disease.

Samir K. Ballas
Thomas Jefferson University

- Acquired Immune Deficiency Syndrome
- Chronic Pulmonary Complications
- Fibromyalgia, Rheumatoid Arthritis and Osteoarthritis
- Gout
- Hepatitis
- Malignant disorders
- Obesity, Diabetes and Hypertension
- Ophthalmological comorbidities
- Orofacial comorbidities
- Otologic comorbidities

"There is concern that the improved survival may be offset by the comorbidities of the older patients in the general population."

Annals of Hematology (2021) 100:2203–2205
https://doi.org/10.1007/s00277-021-04578-w

ORIGINAL ARTICLE

Obesity and diabetes mellitus in patients with sickle cell disease

Tim Jang[1] · George Mo[1] · Connor Stewart[1] · Leen Khoury[1] · Natalie Ferguson[1] · Ogechukwu Egini[1] · John Muthu[1] · Dibyendu Dutta[1] · Moro Salifu[1] · Seah H. Lim[1]

Received: 5 April 2021 / Accepted: 12 June 2021 / Published online: 20 June 2021

n=449

"In this study, we observed that the prevalence of obesity among SCD patients was low."

"[…] type II diabetes mellitus is less common among SCD patients"

Global variability of costs of treatment

blood advances

RESEARCH ARTICLE | MAY 16, 2022

Lifetime medical costs attributable to sickle cell disease among nonelderly individuals with commercial insurance

Kate M Johnson, Boshen Jiao, Scott D Ramsey, M A Bender, Beth Devine, Anirban Basu

WILEY AMERICAN JOURNAL OF HEMATOLOGY

This Article | For Authors | Learn More | Submit

Am J Hematol. 2021 Jan; 96(1): E2–E5. PMCID: PMC7756644
Published online 2020 Oct 6. doi: 10.1002/ajh.26007 PMID: 32974896

Making hydroxyurea affordable for sickle cell disease in Tanzania is essential (HASTE): How to meet major health needs at a reasonable cost

Enrico Costa,[1,2] Prosper Tibalinda,[3] Enrico Sterzi,[1] Hubert M. G. Leufkens,[2] Julie Makani,[4] Eliangiringa Kaale,[3] and Lucio Luzzatto[4]

USA: $1.6-$1.7M per patient

	Availability		Mean Treatment cost (dose: 1,000 mg per day)		Affordability	
	2016	2018	Daily (US$)	Monthly	Mean day-wages to purchase 1 month of treatment	Retail price / IRP Ratio
HASTE	-	-	0.18 (0.16 - 0.20)	5.40 (4.80 - 6.00)	3.86 (3.43 - 4.29)	0.41 (0.36 - 0.45)
Muhimbili Hospital Pharmacy	NA	A	0.66 (0.55 - 0.77)	19.80 (16.50 - 23.10)	14.14 (11.79 - 16.50)	1.50 (1.25 - 1.75)
Pharmacy A	A	NA	1.82 (1.82 -1.82)	54.60 (54.60 - 54.60)	39.00 (39.00 - 39.00)	4.14 (4.14 - 4.14)
Pharmacy B	NA	A	1.14 (0.91 - 1.36)	34.05 (27.30 - 40.80)	24.32 (19.50 - 29.14)	2.58 (2.07 -3.09)

Costa *et al* 2021, *Am. J. Hem.*

Conclusions

- SCD is a global disease with large variability/inequalities

Clinicians/haematologists

- More evidence from LMICs is needed
- More multi-systems studies (multiple complications) are needed

Data scientists/epidemiologists

- More systematic efforts to collate current evidence are needed
- Multi-omics studies might help our understanding of SCD

=> require financial support

Acknowledgements

- Congress chairs and International Scientific Committee
  - Mariane de Montalembert
  - Isaac Odame
- Key collaborators
  - France: Jacques Elion, Brigitte Ranque
  - India: Roshan Colah, Dipty Jain
  - Italy: Lucia di Franceschi, Raffaella Colombatti
  - Kenya: Tom Williams
  - Nigeria: Oby Nnodu, Adelunle Adekile
  - UK: David Rees, Baba Inusa, Imelda Bates, Mark Layton
  - US: Assaf Oron, Dennis Chao, Nicholas Kassebaum

Contact:

f.piel@imperial.ac.uk